

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
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1. AGENCY USE ONLY (Leave blank)		2. REPORT DATE July 2005		3. REPORT TYPE AND DATES COVERED Journal Article - Aviation, Space & Env. Med.
4. TITLE AND SUBTITLE Saccadic Velocity and Pupillary Reflexes During Acclimatization to Altitude (4300m)			5. FUNDING NUMBERS	
6. AUTHOR(S) A. Cymerman, S.R. Muza, A.L. Friedlander, C.S. Fulco, P.B. Rock				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Thermal & Mountain Medicine Division U.S. Army Research Institute of Environmental Medicine Kansas Street Natick, MA 01760-5007			8. PERFORMING ORGANIZATION REPORT NUMBER M05-15	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) Same as #7 above			10. SPONSORING / MONITORING AGENCY REPORT NUMBER	
11. SUPPLEMENTARY NOTES				
12a. DISTRIBUTION / AVAILABILITY STATEMENT Distribution is unlimited.			12b. DISTRIBUTION CODE	
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14. SUBJECT TERMS hypoxia, pupillometry, light reflex, oculometrics, acute mountain sickness			15. NUMBER OF PAGES 8	
			16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unclassified	

# Saccadic Velocity and Pupillary Reflexes During Acclimatization to Altitude (4300 m)

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CYMERMAN A, MUZA SR, FRIEDLANDER AL, FULCO CS, ROCK PB. *Saccadic velocity and pupillary reflexes during acclimatization to altitude (4300 m).* *Aviat Space Environ Med* 2005; 76:627-34.

**Introduction:** Oculometrics have been shown to be responsive to acute hypoxemia. We investigated whether oculometrics could be used as an objective index of a hypoxic effect on the central nervous system (CNS) during altitude acclimatization. We hypothesized that oculomotor reflexes [pupil diameter (PD), constriction amplitude (CA), constriction latency (CL), and saccadic velocity (SV)] changed in concert with a select number of accepted acclimatization variables and that these changes correlated with the severity of acute mountain sickness (AMS). **Methods:** After sea-level, baseline (SLB) measurements were obtained, 18 men (19-33 yr) were transported to Pikes Peak, CO (4300 m), where they remained for 14 d. Periodic measurements (days 1-4, 6, 7, 9, 10, and 12) were made of PD, CA, CL, and SV in addition to heart rate (HR), pulse oximetry ( $SpO_2$ ), end-tidal  $PO_2$  and  $P_{CO_2}$ , 24-h urinary catecholamine concentrations, and AMS severity (environmental symptoms questionnaire, ESQ). **Results:** PD and CL decreased from SLB on days 1-4 and subsequently returned toward SLB; these changes paralleled changes in ventilatory and circulatory variables. CA decreased on days 1 and 2 and remained decreased for 12 d. SV increased over days 1-6 then returned toward SLB with continued exposure, similar to changes in urinary catecholamines. With acclimatization, CL correlated with HR and  $SpO_2$ ; SV correlated with  $P_{CO_2}$ , HR, and  $SpO_2$ . AMS severity peaked during days 2-4, returned toward SLB over the next 10 d, and correlated only with CL ( $p = 0.045$ ). **Conclusions:** Oculometrics can be used as an indicator of CNS hypoxia and altitude acclimatization, although there was no strong correlation with AMS severity.

**Keywords:** hypoxia, pupillometry, light reflex, oculometrics, acute mountain sickness.

THE CENTRAL NERVOUS system (CNS) is particularly sensitive to diminution of the oxygen levels, nutrient supply, and waste removal. With travel to high terrestrial elevations, the reduction in ambient partial pressure of oxygen ( $PO_2$ ) initiates a host of physiological and biochemical responses that attempt to compensate for the oxygen reduction, with the end result being the establishment of acclimatization to a specific, stable altitude. However, before complete acclimatization has occurred, almost all individuals suffer decrements in physical and mental capacities. The initial signs and symptoms of CNS hypoxia are euphoria, hyperventilation, lightheadedness, giddiness, and extroversion. This is temporally followed by headache, insomnia, nausea/anorexia, fatigue, lassitude, dizziness, and malaise (9). The latter are indicative of a complex group of reversible, self-limited symptoms collectively known as acute mountain sickness (AMS). At 4300 m, AMS symptoms

usually do not appear until 6-48 h after arrival and increase in intensity, reaching a peak after 48-72 h, after which they subside over the next 5-7 d. Thus, there appears to be a transition from the initial, direct effect of hypoxia to secondary, indirect, and compensatory responses. Both sets of symptoms are indicative of a disturbance in the "internal milieu" of the CNS, which may be easily quantified by studying selective components of the visual system.

For many years vision has been recognized as being sensitive to hypoxia, with the stimulus for research based on advances in aviation and the need to protect pilots and passengers of high-flying aircraft. Various parameters of visual performance have been studied with exposures to hypoxia (11-13,15,16). These parameters include dark adaptation, night vision, central brightness contrast, color vision, and central acuity, and have a commonality in that they rely to a large extent on volunteer motivation and attention level. Visual tests that are independent of these and other retinal factors are a distinct advantage if they can be shown to relate to subsequent AMS (either as a predictor or an index of severity) and altitude acclimatization. Oculomotor performance and pupillary light reflexes may fill such a role. Thus, there is justification for identifying an objective CNS function that is affected by hypoxia and is correlated to the susceptibility and severity of AMS. In addition, it would be beneficial to determine whether changes in oculomotor responses were congruent with the classical measures of altitude acclimatization.

Changes in arterial oxygen saturation, heart rate, partial pressures of oxygen and carbon dioxide ( $PO_2$  and  $PCO_2$ , respectively) during altitude acclimatization have

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This manuscript was received for review in January 2005. It was accepted for publication in March 2005.

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been well described (20,21). It has also been recognized for many years that altitude stimulates the sympathetic nervous system (2,3,23). All of these variables demonstrate an acute change within minutes or hours, followed by a peak or a nadir after several days, in most cases reaching a level of equilibrium different from that at sea level. Regardless of the direction of change, these temporal changes are considered the classical physiological indices of altitude acclimatization.

Over the years researchers have attempted to define the reasons for the varied AMS susceptibility and also to identify potential risk factors (1,8,17,18,22,24,27). But, to date, no one has been able to predict with reasonable certainty who will become ill and to what extent. It has also been difficult to identify objective, physiological variables that may be associated with illness. Without these relevant objective variables, research studies seeking to evaluate effective pharmaceutical or strategic beneficial interventions are decidedly more difficult. The purpose of this investigation was to study the effects of exposures to high altitude (4300 m, ~459 mmHg) on pupillary reflexes and oculomotor performance in an effort to determine a correlation with: 1) the classic measures of altitude acclimatization; and 2) the severity of AMS.

## METHODS

As part of a research protocol investigating the effect of increased energy expenditure, antioxidant supplementation, and carbohydrate ingestion on work performance and altitude acclimatization to 4300 m altitude, male volunteers were recruited from the vicinity of Palo Alto, CA, during January–April 2002. The protocol was approved in advance by the USARIEM Human Use Research Committee and the U.S. Army Medical Research and Materiel Command's Human Subjects Research Review Board. Each subject provided written informed consent before participating. Requisite inclusion criteria were: 18–35 yr old, non-smokers, normal height-to-weight ratios ( $BMI = 20$ – $27$ ), no large weight changes within the last 6 mo, born below 5000 ft (~1530 m, Denver, CO), residence at or near sea level for 6 mo prior to the study, no ingestion of noninvestigator-approved vitamins and food supplements, and ability to perform cycle exercise for at least 1 h at ~75% of their age-predicted maximal heart rate. Details of the antioxidant supplementation, a mixture of  $\beta$ -carotene,  $\alpha$ -tocopherol, ascorbic acid, selenium, and zinc which was administered 3 wk prior to ascent and during the 14 exposure days, is described by Subudhi et al. (26).

Sea-level, baseline measurements were made at the Palo Alto Veterans Affairs Health Care System, Palo Alto, CA, during May and June 2002 on 18 men (25 yr of age: range 19–33). Subjects were tested an average of seven times over the course of 11 d. Diet, caloric expenditure, and exercise studies are reported elsewhere (6). Every 1–3 d during July and August, one or two subjects were transported to Colorado Springs, CO, where they spent the afternoon, evening, night, and next morning breathing supplemental oxygen (96%) supplied by an oxygen concentrator (AirSep, Buffalo, NY). During their 1.5-h automobile ascent to the U.S. Army

Mahe Memorial Altitude Laboratory, Pikes Peak, CO (4300 m), volunteers breathed 100% bottled oxygen. After reaching the summit and until they completed three consecutive pupillometry/oculomotor tests (~1 h), they breathed from another oxygen concentrator. Volunteers repeated the pupillometry/oculomotor tests 3 h after removal of the supplemental oxygen and periodically during the next 2 wk (days 1–4, 6, 7, 9, 10, and 12). Detailed results of the effects of hypobaric normoxia and acute hypobaric hypoxia are described in a preliminary report (5). Measurements consisted of the oculomotor variables pupil diameter (PD), constriction amplitude (CA), constriction latency (CL), and saccadic velocity (SV) and the classical measures of altitude acclimatization: heart rate (HR); arterial oxygen saturation ( $SaO_2$ ); end-tidal  $PO_2$  and  $PCO_2$ ; and 24-h urinary epinephrine and norepinephrine concentrations. Urinary catecholamines were measured until day 10.

Conditions at the summit within the laboratory averaged  $460 \pm 2$  mmHg,  $20$ – $22^\circ C$ , and 15–20% relative humidity. Ambient illumination levels at Palo Alto and at the summit laboratories were approximately 230–245 lux during testing days.

Oculomotor and pupillary reflexes were measured using the FIT 2000 screener (PML, Inc., Rockville, MD). The FIT 2000 is a self-contained, fully automated Class I medical instrument designed to analyze the eye reflexes for signs of central neurological changes. The instrument can detect changes as small as 0.05 mm in pupil size and eye movements as small as  $1^\circ$ . Subjects determined left or right eye dominance prior to any testing and always used the dominant eye for all measurements. Initial pupil diameter was determined prior to any light flashes. To evoke a pupil reflex, 4–7 controlled, 1-s flashes of constant intensity light were produced, allowing measurement of constriction latency and amplitude. To evoke a measured saccadic eye movement, a lighted target moved along a precise horizontal path that the volunteer followed with his/her dominant eye. The entire sequence of 4 measurements took ~30 s to complete. The mean of three sequences, taken 2–4 min apart, was used as a data point. Measurements at sea level were made between 09:00 and 10:30, before any scheduled exercise tests.

$SaO_2$  and HR were measured by pulse oximetry (Nellcor N-200, Nellcor Inc., Pleasanton, CA) after the volunteers were seated and rested for 10 min. Resting oxygen uptakes and carbon dioxide production were measured using a metabolic cart (True Max 2400, ParvoMedics, Salt Lake City, UT). Urinary catecholamines, norepinephrine, and epinephrine were quantified from 24-h urine collections using alumina extraction (Alko Diagnostics, Holliston, MA) and a high performance liquid chromatography HPLC system (Waters Corp., Milford, MA).

The severity of AMS was assessed using a weighted average score of selected cerebral symptoms determined from the Environmental Symptoms Questionnaire (ESQ). The ESQ is a validated, self-reported, 67-question symptom inventory used to determine the presence and severity of symptoms due to exposures to heat, cold, and hypoxia (25). A weighted factor score of

TABLE I. TEST-RETEST CHARACTERISTICS OF FOUR OCULOMOTOR PUPILLARY REFLEX VARIABLES.

Variable	Slope	Intercept	p	r
PD (mm)	0.84	0.73	< 0.0001	0.91
CA (mm)	0.91	20.3	< 0.0001	0.92
CL (ms)	0.80	0.23	< 0.0001	0.80
SV (mm · s <sup>-1</sup> )	0.46	36.1	= 0.0006	0.54

N = 37 subjects; p = probability value; r = reliability coefficient; PD = pupil diameter; CA = constriction amplitude; CL = constriction latency; and SV = saccadic velocity.

11 subjective symptom scores was used; a value of 0.7 or greater is indicative of the presence of AMS.

Test-retest reliability analyses were performed for the four oculomotor and pupillary parameters (initial PD, CA, CL, and SV) collected at sea level using the FIT 2000. Simple regression analysis was used on previously collected data from 37 subjects from a previous study. Subjects were tested at the beginning and end of a 1-h rest period under sea-level conditions. The degree in which data values are consistent over time is an indication of the variation from testing session to testing session, i.e., variable variability. Coefficient of stability (r) is the measure of test-retest reliability.

Initial analyses used a 2 × 10 repeated measures of analysis of variance (group × time): (antioxidant and placebo × SL, D1, D1.25, D2, D3, D4, D6, D7, D9, D10, D12) with 9 subjects in each group (Sigma Stat, v2.03, SPSS, Chicago, IL). If no significant effect was found due to antioxidant, both groups were combined and treated as one. When significant main effects were found (p ≤ 0.05), post hoc analyses using Dunnett's (for multiple comparisons vs. control) or Tukey's (for all pairwise comparisons) tests were used. Regression analyses of oculomotor performance and pupillary reflexes vs. acclimatization variables (catecholamine excretion, Po<sub>2</sub> and Pco<sub>2</sub>, HR, blood oxygen saturation) were performed using a linear, repeated measures regression test with between subject differences taken into account (7). Dummy variables were used to encode different subjects.

## RESULTS

There were no significant differences found in any of the four measured oculomotor variables (pupil diameter, constriction amplitude, constriction latency, and saccadic velocity) regardless of the group into which

the subjects were placed; therefore, all the subjects were combined into one group. Test-retest reliabilities for all the oculomotor variables are shown in Table I. Data were obtained from a previous study (5). Reliability values for PD, CA, and CL are all similar (0.92 to 0.80). SV showed the worst reliability with an r-value of 0.54. As a further indication of reliability, Cronbach's alpha was calculated (SPSS, Inc., Chicago, IL). Alphas for PD, CA, CL, and SV were 0.95, 0.89, 0.96, and 0.70, respectively. Being 0.7 or higher, all alphas are indicative of good reliability. No test-retest calculations were made at altitude because repeat measurements were made within minutes of each other. During the acclimatization study, the 18 subjects were tested at sea level 3–10 times (mean = 7) in the course of 7–19 d (mean = 11). There was no indication of a learning effect on any of the oculometric measurements.

Since the volunteers were kept on supplemental O<sub>2</sub> from the time of their arrival in Colorado Springs, CO (1800 m), until after completing the FIT measurements on the Pikes Peak summit (4300 m), it was possible to examine whether hypobaria per se had any effect on the oculomotor/pupillary measurements (Table II). There was no reduction in PD, CA, CL, or SV immediately after arriving at 4300 m with supplemental O<sub>2</sub>. There was also no reduction 30 min after terminating supplemental O<sub>2</sub>. The first indication of an effect of hypoxia occurred after 3 h, with significant reductions in PD and CA, only slight, nonsignificant changes occurring in CL, and no changes in SV.

The changes in initial PD and CA during 12 d of continuous exposure to 4300 m are shown in Fig. 1. One subject was removed from the study on day 6 and is not included on Figs. 1–4. Pupil diameter (Fig. 1A) decreased during the first 3 d followed by a return to the initial sea-level baseline values. Constriction amplitude (Fig. 1B) also decreased during the first 2 d but appeared to establish a new, albeit lower stable level evident after 9 and 12 d. As Fig. 2 demonstrates, constriction latency (Fig. 2A) showed a similar response as pupil diameter, decreasing during the first 3 d of exposure followed by a return toward sea-level values. Saccadic velocity (Fig. 2B) never decreased below sea-level values, was significantly elevated from days 2–6, and remained slightly elevated for the remainder of the exposure.

Figs. 3 and 4 illustrate classic changes in Po<sub>2</sub>, Pco<sub>2</sub>, HR, and SaO<sub>2</sub> over the 12 d of altitude exposure. Daily

TABLE II. MEAN (± SE) OF PUPILLARY REFLEXES AND OCULOMOTOR PERFORMANCE OF 18 MALE VOLUNTEERS AT SEA LEVEL (PALO ALTO, CA) AND THE SUMMIT OF PIKES PEAK, CO (PP, 463 MMHG)

Variable	Environmental Condition				
	Sea Level	PP + O <sub>2</sub>	PP 0 h	PP 3 h	PP 24 h
PD (mm)	5.9 ± 0.2	5.9 ± 0.2	5.8 ± .2	5.2 ± 0.3†	5.3 ± 0.2†
CA (mm)	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.0 ± 0.1*	1.1 ± 0.1*
CL (ms)	295 ± 3	302 ± 5	297 ± 4	292 ± 5‡	286 ± 5†
SV (mm · s <sup>-1</sup> )	69 ± 2	68 ± 3	70 ± 3	69 ± 3	72 ± 2

Volunteers received O<sub>2</sub> the evening prior to and during the first measurement (PP + O<sub>2</sub>) that occurred within 0.5 h of attaining the summit. PP 0 h = 30 min without supplemental O<sub>2</sub>. PD = pupil diameter; CA = constriction amplitude; CL = constriction latency; and SV = saccadic velocity. Compared to sea level or PP + O<sub>2</sub>, \* p = 0.01, † p < 0.001, ‡ p = 0.058.

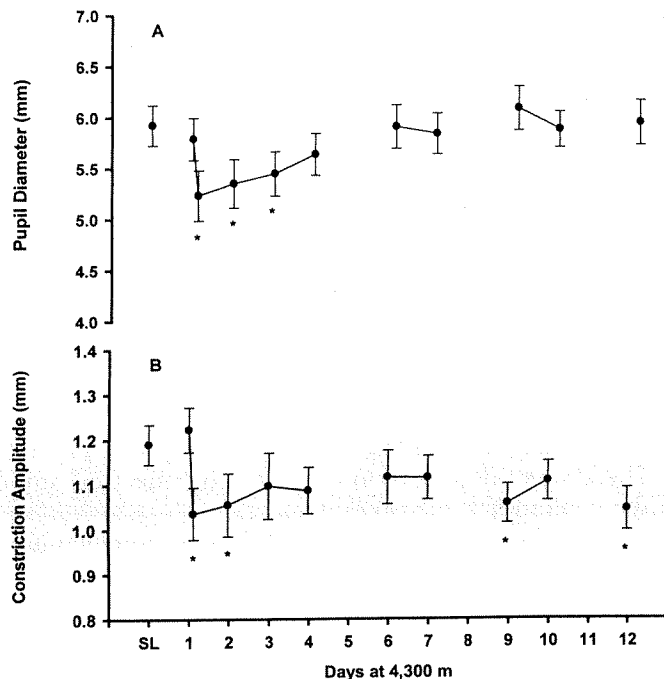


Fig. 1. A) Initial pupil diameters and B) constriction amplitudes measured at sea level, immediately on exposure to 4300 m altitude, and periodically during acclimatization. Values are mean  $\pm$  SE. \* = significantly different from sea level ( $p \leq 0.05$ ),  $n = 17$ .

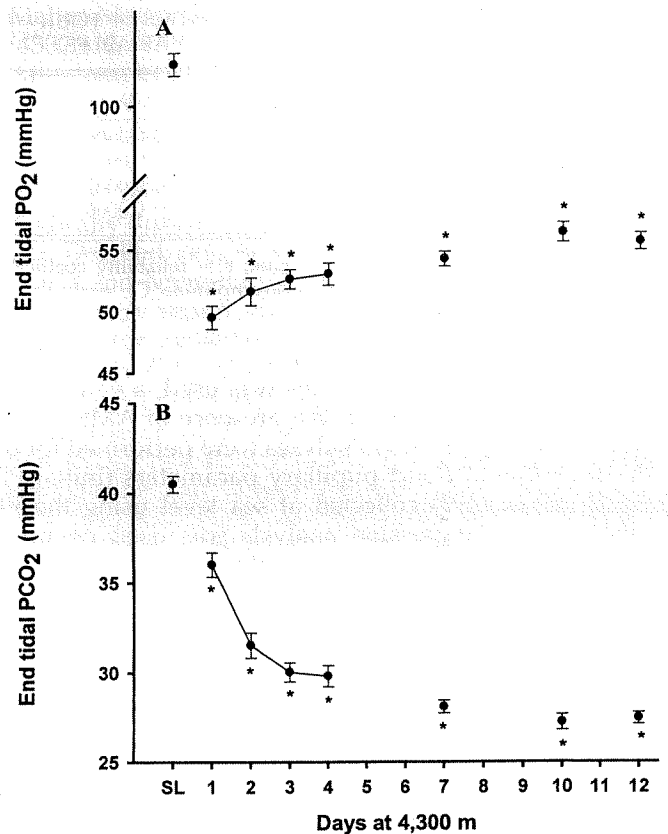


Fig. 3. End-tidal partial pressures of A) O<sub>2</sub> and B) CO<sub>2</sub> at sea level (SL) and during acclimatization to 4300 m altitude. Values are means  $\pm$  SE;  $n = 17$ ; \* = significantly different from sea level,  $p \leq 0.05$ .

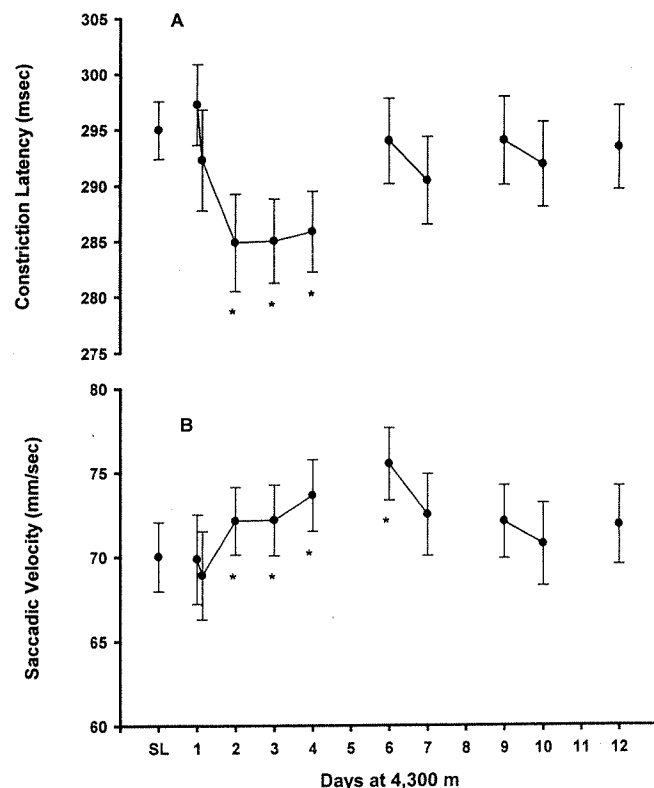


Fig. 2. A) Constriction latencies and B) saccadic velocities measured at sea level, immediately on exposure to 4300 m altitude, and periodically during acclimatization. Values are means  $\pm$  SE. \* = significantly different from sea level,  $p \leq 0.05$ ,  $n = 17$ .

catecholamine excretion levels during continuous exposure to 4300 m altitude are described by Cymerman et al. (4). Respiratory responses show an acute change over the first 4 d followed by the establishment of new plateaus. During 12 of the 14 d of exposure, values never approached their initial sea-level value. Increases in resting HR peaked during days 2–4, followed by a slow decrease toward sea-level baseline values; S<sub>a</sub>O<sub>2</sub> showed similar but reciprocal changes with saturation levels stabilizing at approximately 89% after 10–12 d of exposure. Urinary catecholamine concentrations (not shown) mirrored changes in resting HR with significant increases on days 1–4 (epinephrine, mean  $\pm$  SE: sea level,  $11 \pm 2$ ; altitude,  $27 \pm 5 \mu\text{g} \cdot 24 \text{ h}^{-1}$ ) and 1–5 (norepinephrine, mean  $\pm$  SE: sea level,  $42 \pm 6$ ; altitude,  $261 \pm 51 \mu\text{g} \cdot 24 \text{ h}^{-1}$ ). The remainder of the time, catecholamines were elevated but not significantly different from sea level. The progression and improvement of AMS symptom severity is depicted in Fig. 5. Symptom severity rose on day 1, peaked during days 2–4, and gradually returned toward sea level thereafter.

In order to determine whether the changes observed in oculometrics coincided with changes in the variables classically used to monitor altitude acclimatization, a repeated measures regression method was used so that all the data collected during acclimatization could be used in the analysis. During altitude acclimatization constriction, latency coincided inversely with changes in HR and directly with S<sub>P</sub>O<sub>2</sub>, while saccadic velocity coincided inversely with end-tidal PCO<sub>2</sub> and S<sub>P</sub>O<sub>2</sub> and

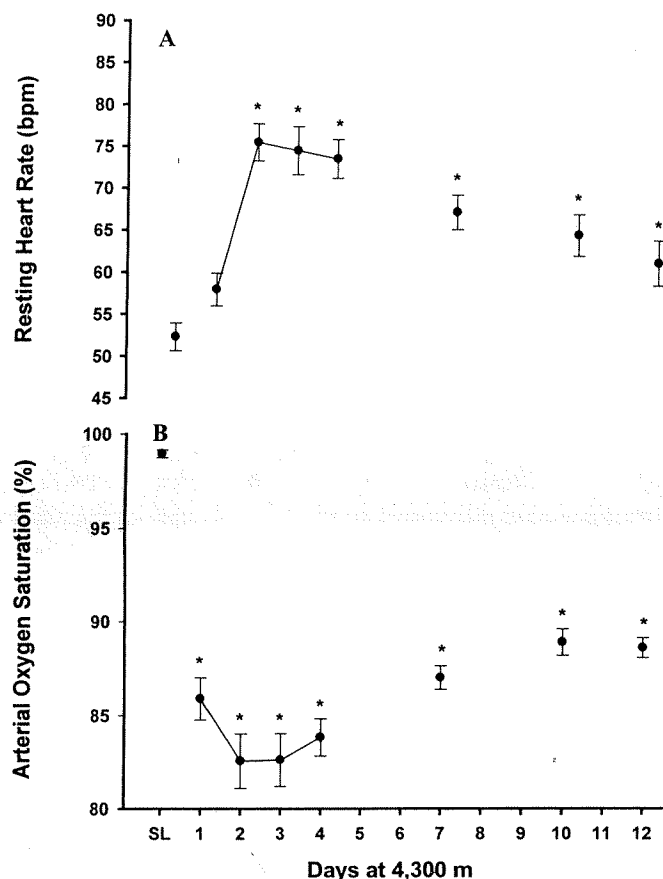


Fig. 4. Changes in A) resting heart rate and B) arterial oxygen saturation during 12 d of exposure to 4300 m. Values are means  $\pm$  SE. \* = significantly different from sea level,  $p \leq 0.05$ ,  $n = 17$ .

directly with end-tidal  $P_{O_2}$  and HR (Table III). There was no correlation of any oculometric variable with urinary epinephrine or norepinephrine.

Repeated measures regression of oculometrics from data obtained on days 2–4 (when AMS was at its severest in most subjects) indicated very little association of oculometrics with the severity of AMS. AMS severity was associated with an increase in CL (coefficient = 0.022,  $t = 2.136$ ,  $p = 0.045$ ) and possibly a decrease in SV ( $p = 0.066$ ). Linear regression analysis of AMS severity on day 3 and all of the oculometric measurements also revealed no correlation, even when analyzed as a difference from sea-level baseline or as a percent change from baseline on day 3.

## DISCUSSION

The objective of the present report was to determine the effect of altitude acclimatization on oculomotor performance and pupillary reflexes. We demonstrated that ocular and pupillary responses are significantly altered by altitude exposure with changes characterized by an acute response over several days followed by stabilization to previous or new baselines. The first 4–6 d of altitude exposure are characterized by decreases in initial PD, CA, and CL. In contrast, SV increased during the same time period. We found no correlation with the severity of AMS. Objective oculomotor measurements

can be used as an indicator of CNS hypoxia as well as an index of acclimatization to altitude.

In order to accomplish the primary objective of this study, it was first necessary to verify that repeated measurements of the four oculomotor variables would be consistent and reliable when performed repeatedly in the same individual. Secondly, in order to increase the statistical power by combining treatment groups (antioxidant and placebo), it was necessary to establish that there were no effects from the primary intervention of the overall research protocol, i.e., that dietary antioxidant supplementation would affect the characteristics of AMS and oculometrics. Our results indicated that measurements of pupillary reflexes and oculomotor performance were consistent and reliable. The test-retest reliability scores for the three pupillary variables were very high with the score for SV slightly lower. In addition, the outcome variables showed excellent stability when measured under normal conditions at the same time of day over the course of several days. There also appeared to be no learning effects associated with any of the variables. Secondly, no significant effect was found between the antioxidant and the placebo groups, allowing us to combine data from all the subjects into one group.

Confirming the results from our previous report (5), we observed that initial PD, CA, and CL were reduced with initial hypoxic exposures ( $> 1$  h), while SVs were increased during the same time period. We extended the time course by observing that the reductions persisted for the first 2–4 d and then returned toward baseline levels, except for CA, which tended to remain reduced for the entire 12 d. SV increased during the first 6 d but then returned toward baseline. These observations tended to follow the changes seen in  $P_{O_2}$ ,  $P_{CO_2}$ , HR, saturation, and catecholamines, i.e., an acute change during the first 2–4 d followed by the establishment of a new stable baseline or a return to levels indistinguishable from baseline. The development and remission of AMS symptoms followed its classical pat-

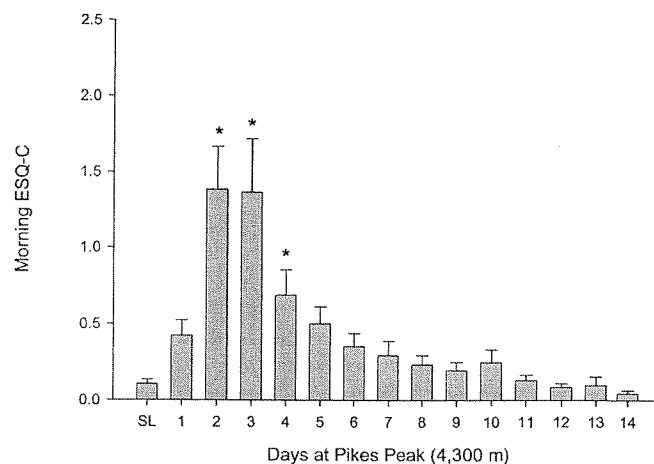


Fig. 5. Acute mountain sickness cerebral symptoms derived from morning environmental symptoms questionnaires (ESQ-C) during acclimatization to 4300 m altitude. \* = significantly different from sea level,  $p < 0.001$ , means  $\pm$  SE,  $n = 18$  ( $< 6$  d);  $n = 17$  ( $> 5$  d). Day 1 =  $\sim 1$  h after removal of supplemental  $O_2$ , which was administered during ascent and initially on the Pikes Peak summit. Day 2 and thereafter are progressive 24-h increments.

TABLE III. SUMMARY OF CORRELATION COEFFICIENTS COMPARING OCULOMOTOR VARIABLES WITH CLASSIC PARAMETERS OF ACCLIMATIZATION DURING THE 1ST 3 D OF EXPOSURE TO 4300 M ALTITUDE.

Acclimatization Variable	PD (mm)		CA (mm)		CL (ms)		SV (mm · s <sup>-1</sup> )	
	Slope ± SE	p	Slope ± SE	p	Slope ± SE	p	Slope ± SE	p
NE (μg · 24 h)	0.00 ± 0.00	ns	0.00 ± 0.00	ns	-0.01 ± 0.01	ns	0.00 ± 0.00	ns
EPI (μg · 24 h)	0.01 ± 0.01	ns	0.00 ± 0.02	ns	0.07 ± 0.14	ns	0.01 ± 0.07	ns
PO <sub>2</sub> (mmHg)	0.01 ± 0.03	ns	0.00 ± 0.01	ns	0.71 ± 0.78	ns	0.80 ± 0.34	0.028
Pco <sub>2</sub> (mmHg)	0.01 ± 0.02	ns	0.00 ± 0.01	ns	0.91 ± 0.53	0.099	-0.81 ± 0.21	0.001
HR (bpm)	0.00 ± 0.01	ns	0.00 ± 0.00	ns	-0.47 ± 0.14	0.003	0.21 ± 0.07	0.006
SpO <sub>2</sub> (%)	0.00 ± 0.02	ns	0.00 ± 0.01	ns	1.52 ± 0.27	0.001	-0.32 ± 0.18	0.009

PD = pupil diameter; CA = constriction amplitude; CL = constriction latency; and SV = saccadic velocity. NE = urinary norepinephrine; EPI = urinary epinephrine; PO<sub>2</sub> = end-tidal partial pressure of oxygen; PCO<sub>2</sub> = end-tidal partial pressure of carbon dioxide; HR = heart rate; SpO<sub>2</sub> = pulse arterial oxygen saturation; ns = not significant.

tern—an increase in ESQ cerebral symptom score after the first day, peaking during days 2–4, followed by a rapid return to baseline.

The question of correspondence of oculometric variables with physiological acclimatization variables may be difficult to assess because no previous studies have attempted to relate oculometrics and altitude acclimatization. There are two papers that describe pupillary changes during acute hypoxia. Van der Post (29) found decreases in saccadic velocity in 12 volunteers exposed to 130 min of a hypoxic gas mixture producing arterial O<sub>2</sub> saturations of ~80%. In patients with different degrees of respiratory insufficiency or during anesthesia, Jordanov and Ruben (10) observed either no change or pupillary contraction within minutes of exposure to arterial PO<sub>2</sub>s as low as 34 mmHg. Our results indicated that all the measured oculometric variables were affected by hypoxia within the first 3–4 d of altitude exposure. Initial PDs and CLs were depressed in the first 24 h (day 2) of exposure, but returned toward normal thereafter. CA remained decreased for almost the entire 12 d. SVs were increased from days 2 to 6, when mean pulse oxygen saturation (SpO<sub>2</sub>) was 83%, but returned to levels indistinguishable from baseline measurements. Catecholamine excretory values were also increased during this period. All these oculometric changes temporally corresponded to the changes in HR, PO<sub>2</sub>, Pco<sub>2</sub>, and SpO<sub>2</sub>, which also showed the greatest changes during the first 4 exposure days. Significant correlative changes were observed between CL and HR and SpO<sub>2</sub>. SV also correlated with changes in Pco<sub>2</sub>, HR, and SpO<sub>2</sub> during acclimatization. Thus, it appears that oculometrics can be used to simply, quickly, and reliably track acclimatization to altitude.

A physiological explanation for these oculometric changes with hypoxic exposure and acclimatization is difficult to provide. There appear to be two phenomena occurring simultaneously: reductions in PDs and CAs indicative of a central depressive effect of hypoxia; and reductions in CLs (faster reaction times) and increased SVs, both of which are indicative of a stimulatory effect. Approaches that can be taken to explain the dichotomy are: a direct, transient, and inhibitory effect of hypoxia on specific components of the central nervous system; an indirect effect due to increases in peripheral neurohumoral factors; or a combination of both occurring at the same time.

A healthy iris is in constant motion even when light

conditions and accommodation are constant. This physiologic pupillary instability or dynamic equilibrium is due to fluctuations in the activity of sympathetic and parasympathetic innervations to the iris muscles. As explained by Thompson (28), when the level of consciousness or alertness is reduced, as may also occur with hypoxia, pupils become smaller and oscillation becomes apparent. This is a reflection of a decrease in inhibition of the Edinger-Westphal nucleus, a parasympathetic component of the oculomotor nucleus, followed by a preponderance of parasympathetic outflow. There is further evidence for a reduction in pupil size with a decrease in level of consciousness, alertness, and acute hypoxia. Morad et al. (19) observed decreases in pupil size with fatigue and subjective feelings of sleepiness. Lowenstein et al. (14) observed that miosis (pupil contraction) is common and light reflexes are markedly reduced when subjects are tired. Thus, the pupillary hypoxic response (miosis) may be analogous to the pupillary response preceding sleep or during fatigue and could result from a decrease in inhibition of a CNS parasympathetic nucleus.

The decrease in the amplitude of the light reflex is coupled to the decrease in pupil diameter in that light reflexes are superimposed on the dynamic equilibrium. This superimposition can be modified by humoral adrenergic factors (i.e., peripheral catecholamines) as well as mechanical limitations of the iris. Peripheral changes in catecholamine levels probably have little effect on pupillary reflexes because their concentrations result primarily from the accumulation of unmetabolized catecholamines and spill-over from neuronal terminals in sympathetic tissues and the adrenal medulla. Thus, plasma and urine levels provide a limited, delayed view of the possible systemic effects at peripheral nerve endings and in the CNS. If PD is sufficiently reduced, it is conceivable that the amplitude of a light response would also be reduced if the ability of the pupil to constrict further is limited. This mechanical contraction limitation is not likely. The mean PD at sea level in our subjects was 5.92 mm and the mean minimum diameter on the first day of altitude exposure was 5.23 mm. Thus, with a normal range of 1 to 9 mm, we do not believe that a mechanical limitation was present. Nevertheless, the same flash stimulus could elicit a smaller response if a nonlinear length-tension relationship is involved. Therefore, at the present time,

we cannot explain the decrease in initial PD and the decrease in flash-produced CA that occurs during altitude acclimatization.

It is possible that peripheral catecholamines could affect specific pupillometric measurements. The changes observed in CLs and SVs are indicative of a stimulation of the sympathetic nervous system, i.e., reaction times were faster (shorter CLs) and increased SVs. SV, as measured by the FIT 2000, is the outcome movement of a horizontal, voluntary reflex arc involving simultaneous contraction and relaxation of agonist and antagonist muscles (medial and lateral recti muscles). These muscles, being extraocular and striated, may be more easily affected by increases in blood-borne catecholamines (as reflected by excretory increases in both epinephrine and norepinephrine). Both CL and SV were significantly correlated with HR and  $SpO_2$ ; SV was also correlated with end-tidal  $P_{CO_2}$ . However, there was no correlation of any of the oculometric measurements with urinary catecholamines, possibly because of the relatively large variance associated with urinary excretory values.

Although the progression of AMS severity showed classic quantitative and temporal changes with altitude acclimatization at 4300 m (9), we were unable to demonstrate any strong correlation with measured oculometrics. In a previous study, we were able to show that the decrease in pupil diameter was correlated with the decrease in  $SaO_2$  (5), and low  $SaO_2$  has been correlated with subsequent severity of AMS (24). Nevertheless, we were unable to correlate changes in PDs to changes in AMS even though the majority of subjects (10 of 18 on altitude day 3) indicated they had symptoms severe enough to be considered AMS. In fact, we were only able to demonstrate a significant positive correlation of AMS severity with CL and a possible negative correlation with SV. It should be noted that the study was powered for the primary objective, and we cannot rule out that we would have seen further significant effects if we had used an appropriately powered sample size for this secondary objective.

## CONCLUSIONS

A host of respiratory, cardiovascular, endocrine, and neuroendocrine changes are invoked by ascent to high terrestrial altitudes. Ocular and pupillary responses also appear to be affected by hypoxia with changes characterized by an acute response over several days followed by stabilization to a previous baseline or the establishment of a new baseline. The first 4–6 d of exposure are characterized by decreases in initial PD, CA, and CL. In contrast, SV, an extraocular, striated muscle function, increases during the same time period. The latter two variables may represent an indirect effect due to increased sympathetic activity while the former two variables may be associated with a direct effect of hypoxia on the CNS. Quick, simple, and objective oculometric measurements can be used as an indicator of CNS hypoxia and as an additional index of altitude acclimatization, even though there was no strong correlation with AMS severity.

## ACKNOWLEDGMENTS

The authors wish to thank the volunteers for their willingness to endure the difficulties of high altitude exposure and the research procedures they were asked to perform. We also wish to thank the numerous support staff who contributed directly and indirectly to the support of this project: Dr. Beth Beidleman, SGT Tommy J. Bruington, SSG Dan T. Ditzler, LTC Ann Grediagin, Erik Lammi, Sharon K. Lesh, SPC Mona M. Mathow, SPC Jack E. Mazzotti, SGT Dennis M. Rufolo, Tracey J. Smith, Robert Soares, Janet E. Staab, SGT Stephen M. Watt, and Frank Zirpolo. Special thanks are given to Mr. Mark Sharp and SSG David DeGroot, who ensured that the Pikes Peak Laboratory was made operational and safe, and to Dr. Gary Kamimori for his analysis of urinary catecholamines. Dr. Robert F. Wallace kindly provided expertise on the statistical analysis and interpretation of the data.

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